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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,781	07/21/2000	Paul B. Fisher	61150/JPW/JML	4970

7590 06/17/2002

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EXAMINER	
LOEB, BRONWEN	
ART UNIT	PAPER NUMBER
1636	13

DATE MAILED: 06/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/621,781	FISHER ET AL.	
	Examiner	Art Unit	
	Bronwen M. Loeb	1636	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *15-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to the communication filed 1 April 2002.

Claims 1-37 are pending.

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-14, in Paper No. 12 is acknowledged.

2. Claims 15-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Sequence Compliance

3. The Office has corrected minor errors in the computer readable format. Specifically, non-ASCII "garbage" at the beginning of the file was deleted. Applicant does not need to take any action with respect to this information.

Drawings

4. Applicant's attention is drawn to the attached Form 948, Draftsperson's Review of the Drawings.

5. The drawings are objected to because in Figure 2, the +1 site is shown above an A, which would make the AP-1 site nucleotides +5 to +11. However, the specification refers to the AP-1 site as being nucleotides +6 to +12. See for instance p. 8, lines 1-4 and claim 3. A proposed drawing correction or corrected drawings are required in reply

to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Specification

6. The abstract of the disclosure is objected to because it exceeds 150 words in length. Correction is required. See MPEP § 608.01(b).

7. The disclosure is objected to because of the following informalities: On p. 45, line 17, there is a reference to a fragment deleted from –1287 however the apparently corresponding fragment shown in Figure 5 (fragment #11) is deleted from -1167. On p. 45, line 9 there is a reference to a deletion from –1267 to –536 however the apparently corresponding fragment in Figure 5 (fragment #6) is deleted from –1267 to –361.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 2-14 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is based on the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. §112, first paragraph "Written Description" Requirement published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). Claim 2 is drawn to an isolated nucleic acid comprising a fragment of the nucleotide sequence of claim 1 which is at least 15 nucleotides in length. This is a genus claim in terms of any nucleotide sequence of 15 nucleotides which is a fragment of the nucleotide sequence comprising –270 to +194 of SEQ ID No. 1. The specification mentions various deletion and truncation mutants, all of which are much larger than 15 nucleotides. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all isolated nucleotide sequences at least 15 nucleotides in length based on the teachings in the specification. The specification teaches that the PEA3 site at –104, the AP1 sties at +8 and the TATA box at –24 are the primary determinants of basal promoter activity (p. 45). No 15 nucleotide fragment could contain all three of these sites, thus no 15 nucleotide fragment is expected to have promoter activity. Furthermore, given that in claim 1, the claim language is open, the 15 nucleotide fragment may not be from the fragment of SEQ ID No. 1 from –270 to +194 at all and could be any sequence at all. Therefore, the specification does not describe the claimed isolated nucleic acids comprising a fragment of the nucleotide sequence of claim 1 which is at least 15 nucleotides in length in such full, clear, concise and exact terms so as to indicate that Applicant has possession of these isolated nucleic acids at

the time of filing the present application. Thus, the written description requirement has not been satisfied.

10. Claims 2-5 and 7-14 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for an isolated nucleic acid comprising a fragment of the nucleotide of claim 1 which is at least 15 nucleotides in length and which has PEG-3 promoter activity, does not reasonably provide enablement for an isolated nucleic acid which does not have PEG-3 promoter activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 2 encompasses any isolated nucleic acid comprising a fragment of the nucleotide sequence of claim 1 which is at least 15 nucleotides in length.

The nature of the invention is a promoter from a particular progression elevated gene (PEG-3) identified in rat cells.

An analysis of the prior art as of the effective filing date of the present application does not teach a use for an isolated nucleic acid that is a fragment of the PEG-3 promoter that is at least 15 nucleotides in length and does not have promoter function.

The relative skill of those in the art of mammaliam promoters is high.

The area of the invention is unpredictable as it is entirely unknown what function the claimed isolated nucleic acid might have if it does not promoter activity.

The present specification provides no guidance on how to use the claimed genus of nucleic acids. The specification discloses no uses for an isolated nucleic acid of at least 15 nucleotides in length which is a fragment of nucleotides -270 to +194 of SEQ ID No. 1 which lacks promoter activity.

There are no working examples disclosed that disclose a use the claimed isolated nucleic acid other than as a promoter.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed isolated nucleic acid. In order to determine how to use the isolated nucleic acid, one of skill in the art would have to determine what function, if any, it has and then determine if there is a use for it. Since neither the prior art nor the specification provides the answers to these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue

experimentation by one of skill in the art to determine how to use the claimed isolated nucleic acids.

11. Claims 10-14 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction of guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The present claims are very broad. Claim 10 encompasses isolated nucleic acid comprising a fragment of the PEG-3 promoter comprising nucleotides -270 to +194 of SEQ ID No. 1 which is linked to a tumor suppressor gene, a gene whose expression causes apoptosis of a cell or a cytotoxic gene.

The nature of the invention is an isolated nucleic acid comprising a fragment of the PEG-3 promoter comprising nucleotides -270 to +194 of SEQ ID No. 1 which is linked to a tumor suppressor gene, a gene whose expression causes apoptosis of a cell or a cytotoxic gene, a vector comprising the isolated nucleic acid or any host cell comprising the vector. The only use for these products disclosed in the specification is

gene therapy. See for instance: p. 22, lines 9-18; p. 25, lines 17-26; p. 27, lines 4-10; p. 27, line 26- p. 30, line 32; and p. 36, line 15 - p. 37, line 5.

An analysis of the prior art as of the effective filing date of the present application shows the complete lack of documented success for any treatment based on gene therapy. In a review on the current status of gene therapy, both Verma et al (Nature (1997) 389:239-242) and Palù et al (J. Biotechnol. (1999) 68: 1-13) state that despite hundreds of clinical trials underway, no successful outcome has been achieved. See Verma et al, p. 239, 1st paragraph; Palù et al, p. 1, Abstract. The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient. See p. 33, Abstract and col. 1, 1st and 2nd paragraphs. While all three references indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. See Verma et al, p. 242, col. 2-3; Palù et al, pp. 10-11; Luo et al , p. 33, col. 1, 1st paragraph.

The relative skill of those in the art of gene expression in vivo is high.

The area of the invention is unpredictable. As discussed above, the method of in vivo or ex vivo gene therapy is highly complex and unpredictable. Indeed, the recent tragic and unexpected death of a participant in a gene therapy clinical trial clearly

illustrates the unpredictable nature of gene therapy. See Fox, ASM News, Feb. 2000, 66 (2): 1-3. The skilled artisan at the time the present invention was made recognized the difficulty of achieving sufficient heterologous gene expression to induce any therapeutic effect.

The present specification provides little or no guidance to support the claimed invention for gene therapy applications. The specification discloses no specific therapeutic molecules and diseases to which the claimed isolated nucleic acid can be applied. Furthermore, while the PEG-3 promoter was identified in progression-elevated cells in rats and has a differential expression pattern depending on the extent of progression (as characterized by anchorage independence and tumorigenic potential), there is no evidence that the promoter would function the same way in any other mammalian cells, such as humans. There is no direction provided as to how to overcome the obstacle to gene therapy recognized by leaders in the field, i.e. low efficiency of gene delivery and transient gene expression.

There are no working examples disclosed which encompass gene therapy.

The quantity of experimentation necessary to carry out the claimed invention is high as the skilled artisan could not rely on the prior art or the present specification to teach how to use the claimed methods. In order to determine how to use the method to treat a condition, one of skill in the art would have to the pattern of expression of the rat PEG-3 promoter in any particular cancer cell type to determine if there is differential expression correlating to the progression status of the cancer cell, determine what effect exogenous transgene expression would have in any cell type, whether the effect could

be exploited for treatment of a disease, how to deliver the given nucleic acid to the appropriate target cells with specificity and efficiency, and how to get sufficient expression to induce at least some therapeutic effect. Since neither the prior art nor the specification provides the answers to all of these questions, it would require a large quantity of trial and error experimentation by the skilled artisan to do so.

Based on the broad scope of the claims, the unpredictability in the area of the invention, the lack of sufficient guidance or working examples in the specification and the quantity of experimentation necessary, it would clearly require undue experimentation by one of skill in the art to determine how to use the claimed isolated nucleic acid comprising a fragment of the PEG-3 promoter comprising nucleotides -270 to +194 of SEQ ID No. 1 which is linked to a tumor suppressor gene, a gene whose expression causes apoptosis of a cell or a cytotoxic gene, a vector comprising the isolated nucleic acid or any host cell comprising the vector.

12. The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-14 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in reciting "the guanosine at position -270 and ending with the cytosine at position +194 of SEQ ID No. 1". SEQ ID No. 1 is a nucleotide sequence of 1970 nucleotides, as listed in the sequence listing. While the numbers recited in the claim appear to relate to Figure 2, the numbering is inconsistent

with the sequence listing. The numbering for the recited section with respect to SEQ ID No. 1 appears to be nucleotides 1507 to 1770.

Claim 3 is vague and indefinite in reciting "position -105 and ending with the thymiding at position -100", "position -29 and ending with the adenosine at position -24" and "position +6 and ending with the adenosine at position +12". SEQ ID No. 1 is a nucleotide sequence of 1970 nucleotides, as listed in the sequence listing. While the numbers recited in the claim appear to relate to Figure 2, the numbering is inconsistent with the sequence listing for SEQ ID No. 1.

Claim 3 is vague and indefinite in reciting "the thymidine at position +6" and "the adenosine at position +12". In Figure 2, however, both position +6 and position +12 are guanosine. Therefore the metes and bounds of the claim cannot be ascertained.

Claim 7 is vague and indefinite because it is unclear what it means to have an isolated nucleic acid of claim 2 operably linked to a gene of interest when the isolated nucleic acid of claim 2 does not has promoter activity. What operation is referred to in this recitation?

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application

by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 4102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. §122(b). Therefore, this application is examined under 35 U.S.C. §102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. §102(e)).

15. Claims 2-4 and 6 are rejected under 35 U.S.C. §102(b) as being anticipated by Hollander et al (Journal of Biological Chemistry (1997) 272:13731-13737). Hollander et al teach an isolated nucleic acid comprising a promoter sequence of mouse *gadd34* comprising the PEA3 site and the TATA box of SEQ ID No. 1 and has a fragment of at least 15 nucleotides of SEQ ID No. 1. See the attached alignment (Hollander et al. Database GenEMBL. Accession number U83984, 7 July 1998. Accessed 6 April 2002). The nucleic acid has activity as a promoter. See entire document, especially Figure 4.

16. Claims 2-14 are rejected under 35 U.S.C. §102(b) as being anticipated by Fisher et al (WO 98/42315). Fisher et al teach an isolated nucleic acid comprising a PEG-3 promoter. As shown in the attached sequence alignment from the Geneseq database (Fisher et al. Database GENESEQ. Accession number AAV65766, 2 February 1999. Accessed 6 April 2002) the promoter taught by Fisher et al is identical, except for three nucleotide differences, to the fragment of SEQ ID NO. 1 recited in claim 1. The promoter comprises the PEA3 site, the TATA element and the AP1 site. Operably linking the promoter to a gene of interest, such as luciferase or a gene that causes

apoptosis of a cell, is taught. A vector comprising the promoter and a gene of interest is taughts, as is a tumor comprising the vector. See entire document, especially: Figures 14-17 and 24-31; p. 5, lines 5-10; p. 7, lines 32-34; p. 12, lines 8-13; p. 27, line 27-p. 28, line 28; p. 28, line 33- p. 29, line 13; p. 31, lines 13-18; p. 33, lines 9-19; p. 39, line 23-p. 40, line 8; p. 41, line 26-p. 42, line 8; pp. 69-73; p. 138, line 29-p. 140, line 14; pp. 143-147; and p. 167, line 25-p. 168, line 30.

Conclusion

Claims 1-14 are rejected. Claim 1 is free of prior art. The closest prior art, Fisher et al (WO 98/42315) does not teach or suggest the PEG-3 promoter comprising nucleotides 1507-1770 of SEQ ID No. 1.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bronwen M. Loeb whose telephone number is (703) 605-1197. The examiner can normally be reached on Monday through Friday, from 10:00 AM to 6:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than the next business day after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel, can be reached on (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Tracey Johnson, Patent Analyst whose telephone number is (703) 305-2982.

Bronwen M. Loeb, Ph.D.
Patent Examiner
Art Unit 1636

June 17, 2002

JAMES KETTER
PRIMARY EXAMINER